How do rules for signaling generate or constrain biological organization and diversity?

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Signaling is critical to biological function across levels of organization, including communication within or among cells, tissues, organisms, populations, and different species within a community. *We propose that identifying fundamental principles of signaling that underlie information transfer and response across biological scales will enable critical insights into the origins of biological diversity and organizational complexity.* While a rich complexity of signaling processes has been identified, we lack a unified and integrated framework for investigating/understanding signaling across levels of organization and signaling modalities. This is an impediment to uncovering common rules. In particular, there seems to be a break in considering signaling and signal propagation at levels within an organism vs. levels between organisms.

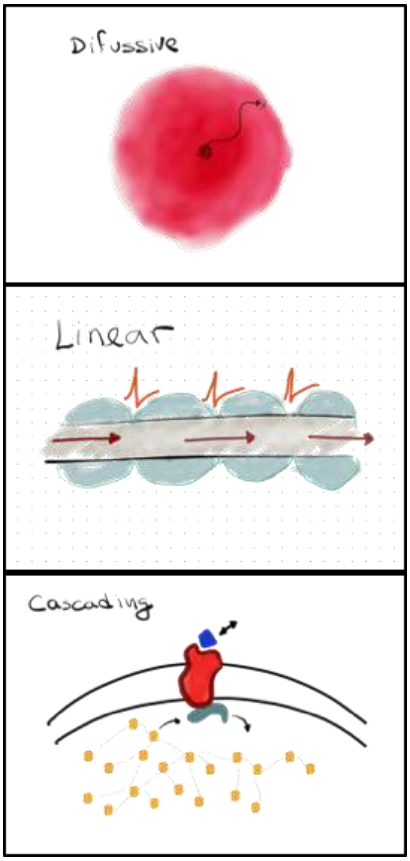

Figure 1. Modes of signaling

Signals provide information about properties that change over space (such as chemical gradients) and/or time. On a molecular level, these may be driven by protein interactions, or interactions of proteins with small molecular ligands. As molecules become organized into cells and increasingly compartmentalized into tissues, organs, and systems, endocrine, paracrine and neural communication allow signals to travel over larger distances to affect specialized targets (e.g., hormonal target tissues) and enable rapid responses. In some cases, specialized mechanisms have developed to discriminate, amplify and propagate signals. Organisms perceive signals from the environment through sensory systems which, once integrated, produce cohesive and wide-ranging effects. Signals may be transmitted within or between species through chemicals (e.g., pheromones or kairomones), sounds, visual signals, or other modalities. The underlying mechanisms enabling signaling within microbial communities and between hosts and their associated microbiome are only beginning to be elucidated. As such, this represents a unique opportunity to further define novel signaling events across biological scales.

On the general rules of signaling and information transfer:
The evolution of signaling mechanisms occurs within a common set of constraints, such as rates of diffusion, speed of sound propagation, and light attenuation. These constraints define the limits of energy “space” under which the evolution of signaling systems takes place. Thus, they provide the context in which the diversity of mechanisms to transmit and detect information may arise. Indeed, the transition from simple diffusive signaling (intrinsically limiting in terms of scale and kinetics) toward true propagation (Figure 1) represents a key transition at multiple scales in the evolution of different life forms. Considerations of the potential effects of gradients, affinity, specificity, inhibition and feedback further impact signal complexity. It is worth asking whether the development of chemical “cascades” (as in GPCR signaling) common in most eukaryotic cells has mechanistic commonalities with organismic-level signaling, as in alarm calling in many vertebrates, quorum sensing in bacteria (chemical/external), or cold acclimation in vertebrates, invertebrates and plants (via environmental cues).

Signaling incurs costs to energy and fitness. Biosynthetic enzymes are costly to synthesize and process (glycosylation, hydroxylation, etc), require co-factors, and are sensitive to pH and temperature. Steroids and prostaglandins require several biosynthetic steps and are relatively costly to produce. In contrast, amino acids such as glutamate and GABA are relatively simple and energetically inexpensive to produce. Energetic costs can also be associated with detecting or amplifying signals (e.g., through molecular receptors or sensory structures). On an ecological level, signals may be shaped by trade-offs between maximizing the likelihood of reproduction at the potential cost of revealing their presence to predators and/or competitors. Thus, there can be selective pressure both to specifically target signals to the desired recipients and avoid detection by predators and competitors. For example, the dramatic plumage of male peacocks provides a strong visual signal to potential mates but provides less visual contrast to common predators with dichromatic vision. Signals can also be mimicked, masked or otherwise disrupted, creating a selective pressure toward improving mechanisms for discriminating meaningful information from noise and false signals (Box 2).

Ultimately, we aim to gain an integrative understanding of the “rules” that govern how signals are transmitted and detected to convey meaningful information across scales of biological organization. For example, can quantitative models or other theories developed at one scale can be applied more broadly across scales? How might models and terminology be expanded or modified to be broadly applicable? Finally, while this vision paper does not explicitly consider transfer of genetic or epigenetic information across generations, there may be something to be learned from these types of information transfer as a type of signal that propagates within organisms and across generations.

Box 1: Additional examples of signaling

- endocrine and nervous signaling within an organism
- tissue-level angiogenesis/tumorigenesis
- hydration state/osmotic pressure (cell volume)
- pressure at organismal (baroreceptors) and molecular levels (activation volumes)
- membrane tension
- immune surveillance
- pathophysiological conditions (pain, anaphylaxis)
- O_2/pH/CO_2 (chemoreceptors) at molecular and organismal levels
- physical properties of the environment: temperature; light intensity and spectral quality (photoreception)
- microbial quorum sensing
- microbiome-host signals
- microbial biofilms as settlement cues for invertebrates

Box 2: Some consequences of signal disruption

- autoimmunity
    - Plant autoimmunity resulting from immune receptors mis-activating)
    - Multiple sclerosis and other autoimmune neurological diseases
- disruption of mammalian reproduction and other steroid signalling by phytoestrogens
- environmental noise masking acoustic communication
- cell growth signaling disruption leading to cancer

What's the potential impact?

We expect that addressing this question will reveal rules of life that span levels of biological organization, or reveal where such rules are absent in the domain of signaling. Work on this question could provide new perspectives and frameworks to study signaling and signal processing in different systems. An understanding of 'rules of signaling' could be used to gain insights into a range of topics including: evolutionary processes, biological innovation, the development of complex and highly organized structures (e.g., central nervous system), the capacity of organisms to respond to a changing environment, species diversity, community structure and dynamics.

Why now?

We believe this is a tractable question to catalyze "reintegration" across biology and beyond. Newly available tools can enable advances in understanding. As one example, high-throughput sequencing has dramatically improved our knowledge of the composition of microbial communities. Thus, by coupling this genetic information with sensitive and high resolution methods of chemical sensing, we can learn more about signaling between microbiomes and their hosts.

State-of-the-art technologies and applications

Cost-effective methods for comparing biological responses to a stimulus, stressor, disturbance etc. that results in signal generation and transmission are now available at multiple levels of biological organization (transcriptomics, proteomics, metabolomics, phosphoproteomics, etc). High-throughput screening approaches allow rapid identification of protein-protein and protein-ligand interactions. Improvements in remote sensing technologies have allowed for real-time biologging and measurement of a limited set of physiological parameters and animal behaviors within the context of their environment.

However, it is expected that methodological advances will be necessary to fill "gaps" in accessible scales of measurement and observation. For example, new instrumentation may be necessary to measure/quantify signals at scales or modalities that are currently poorly understood. Although a great deal of progress has been made in the development of experimental techniques across different biological scales (e.g., genomics, imaging, ecosystem monitoring), we are mindful of a number of gaps still present when transitioning between scales. For instance, integration of imaging/structural insights at the molecular, cellular, organismal and community scales continues to be challenged by the existing gaps between each scale level. This is also the case when considering multiple time scales. Real-time monitoring of signaling and integration with corresponding biochemical, physical, physiological and/or behavioral responses is not yet feasible for all organisms. Strategies of integrating multiple "omics" approaches across scales that require computational methods and big data management have not yet fully emerged. Enhanced computational modeling capacities and emerging AI capabilities may enable more comprehensive integration between organizational levels.

Challenges and opportunities toward re-integrating biology

Addressing this question will require integration across biological disciplines, including biochemistry, biophysics, cell and molecular biology, physiology, behavior, and ecology. Thus, it provides an excellent question around which to focus re-integration of research. This research question will also require integration with other fields including physics, chemistry, mathematics and computer science, and necessitate truly integrative work across levels of organization and space/time scales. To meet these challenges, support and potentially training for this collaborative and integrative science will be critical.

Intended audience of the paper

Pursuing the answers to the central question posed in this vision paper, "*How do rules for signaling generate or constrain biological organization and diversity?"* is critical for understanding the Rules of Life, and therefore, is central to biological research at every level of biological organization/scale. Thus, we believe that there will be broad interest in and support of this proposal from biologists within every biological sub-discipline.